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# PRINCIPLES AND PRACTICE OF INFECTIOUS DISEASES

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THIRD EDITION

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**CHURCHILL LIVINGSTONE**  
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190. *Neisseria Gonorrhoeae* 1613  
*H. Hunter Handsfield*
  191. *Other Gram-Negative Cocci* 1632  
*Dieter H. M. Gröschel*
- GRAM-NEGATIVE BACILLI**
192. *Vibrio Cholerae* 1636  
*William B. Greenough III*
  193. *Other Pathogenic Vibrios* 1646  
*Charles C. J. Carpenter*
  194. *Campylobacter Species* 1649  
*Martin J. Blaser*
  195. *Enterobacteriaceae* 1658  
*Barry I. Eisenstein*
  196. *Pseudomonas Aeruginosa* 1673  
*Matthew Pollack*
  197. *Pseudomonas Species (Including Melioidosis and Glanders)* 1692  
*Jay P. Sanford*
  198. *Acinetobacter Species* 1696  
*David M. Allen and Barry J. Hartman*
  199. *Salmonella Species (Including Typhoid Fever)* 1700  
*Edward W. Hook*
  200. *Shigella Species (Bacillary Dysentery)* 1716  
*Herbert L. DuPont*
  201. *Haemophilus Influenzae* 1722  
*E. Richard Moxon*
  202. *Haemophilus Species* 1729  
*W. Lee Hand*
  203. *Gardnerella Vaginalis* 1733  
*Carol A. Spiegel*
  204. *Brucella Species* 1735  
*Dennis J. Mikolich and John M. Boyce*
  205. *Francisella Tularensis (Tularemia)* 1742  
*John M. Boyce*
  206. *Pasteurella Species* 1746  
*John M. Boyce*
  207. *Yersinia Species (Including Plague)* 1748  
*Thomas Butler*
  208. *Bordetella Species* 1756  
*Erik L. Hewlett*
  209. *Streptobacillus Moniliformis (Rat-Bite Fever)* 1762  
*Ronald G. Washburn*
  210. *Legionella Pneumophila (Legionnaires' Disease)* 1764  
*Victor L. Yu*
  211. *Other Legionella Species* 1774  
*Guo-Dong Fang and Victor L. Yu*
  212. *Other Gram-Negative Bacilli* 1782  
*John E. McGowan, Jr., and Carlos Del Rio*
- SPIROCHETES**
213. *Treponema Pallidum (Syphilis)* 1794  
*Edmund C. Tramont*

214. *Treponema Species (Yaws, Pinta, Bejel)* 1808  
*Jeffrey D. Chulay*
215. *Leptospira Species (Leptospirosis)* 1813  
*W. Edmund Farrar*
216. *Borrelia Species (Relapsing Fever)* 1816  
*Warren D. Johnson, Jr.*
217. *Borrelia Burgdorferi (Lyme Disease, Lyme Borreliosis)* 1819  
*Allen C. Steere*
218. *Spirillum Minor (Rat-Bite Fever)* 1827  
*Ronald G. Washburn*

#### ANAEROBIC BACTERIA

219. *Anaerobic Bacteria: General Concepts* 1828  
*John G. Bartlett*
220. *Clostridium Tetani (Tetanus)* 1842  
*Thomas R. Cate*
221. *Clostridium Botulinum (Botulism)* 1847  
*William Schaffner*
222. *Gas Gangrene (Other Clostridium-Associated Diseases)* 1850  
*John G. Bartlett*
223. *Bacteroides Species* 1860  
*Dori F. Zaleznik and Dennis L. Kasper*
224. *Anaerobic Cocci* 1867  
*John G. Bartlett*
225. *Anaerobic Gram-Positive Nonsporulating Bacilli* 1869  
*John G. Bartlett*

#### MISCELLANEOUS BACTERIA

226. *Bartonella Bacilliformis (Bartonellosis)* 1870  
*Norbert J. Roberts, Jr.*
227. *Calymmatobacterium Granulomatis (Donovanosis, Granuloma Inguinale)* 1872  
*Gavin Hart*
228. *The Agent of Cat Scratch Disease* 1874  
*Gerald W. Fischer*

#### MYCOBACTERIAL DISEASES

229. *Mycobacterium Tuberculosis* 1877  
*Roger M. Des Prez and Craig R. Heim*
230. *Mycobacterium Lepae (Leprosy)* 1906  
*Ward E. Bullock*
231. *Other Mycobacterium Species* 1914  
*W. Eugene Sanders, Jr., and Edward A. Horowitz*

#### DISEASES DUE TO HIGHER BACTERIA

232. *Nocardia Species* 1926  
*Phillip I. Lerner*
233. *Actinomyces and Arachnia Species* 1932  
*Phillip I. Lerner*

#### SECTION F. MYCOSES

234. *Introduction* 1942  
*John E. Bennett*

235. *Candida Species* 1943  
*John E. Edwards, Jr.*
236. *Aspergillus Species* 1958  
*John E. Bennett*
237. *Agents of Mucormycosis and Related Species* 1962  
*Alan M. Sugar*
238. *Sporothrix Schenckii* 1972  
*John E. Bennett*
239. *Agents of Chromomycosis* 1975  
*Kenneth F. Wagner*
240. *Agents of Mycetoma* 1977  
*El Sheikh Mahgoub*
- 241. *Cryptococcus Neoformans* 1980  
*Richard D. Diamond*
- 242. *Histoplasma Capsulatum* 1989  
*James E. Loyd, Roger M. Des Prez, and Robert A. Goodwin, Jr.*
243. *Blastomyces Dermatitidis* 1999  
*Stanley W. Chapman*
244. *Coccidioides Immitis* 2008  
*David A. Stevens*
245. *Dermatophytosis and Other Superficial Mycoses* 2017  
*R. J. Hay*
246. *Paracoccidioides Brasiliensis* 2028  
*Angela Restrepo M.*
247. *Miscellaneous Fungi* 2031  
*John E. Bennett*

## SECTION G. PROTOZOAL DISEASES

248. *Introduction* 2035  
*Jonathan I. Ravdin*
249. *Entamoeba Histolytica (Amebiasis)* 2036  
*Jonathan I. Ravdin and William A. Petri, Jr.*
250. *Free-Living Amebae* 2049  
*William A. Petri, Jr., and Jonathan I. Ravdin*
251. *Plasmodium Species (Malaria)* 2056  
*David J. Wyler*
252. *Leishmania Species: Visceral (Kala-Azar), Cutaneous, and Mucosal Leishmaniasis* 2066  
*Richard D. Pearson and Anastacio de Queiroz Sousa*
253. *Trypanosoma Species (American Trypanosomiasis, Chagas Disease): Biology of Trypanosomes* 2077  
*Louis V. Kirchhoff*
254. *Agents of African Trypanosomiasis (Sleeping Sickness)* 2085  
*Louis V. Kirchhoff*
255. *Toxoplasma Gondii* 2090  
*Robert E. McCabe and Jack S. Remington*
256. *Pneumocystis Carinii* 2103  
*Peter D. Walzer*
257. *Giardia Lamblia* 2110  
*David R. Hill*
258. *Trichomonas Vaginalis* 2115  
*Michael F. Rein*

259. *Babesia* 2119  
*Jeffrey A. Gelfand*
260. *Cryptosporidium and Other Protozoa Including Isospora, Sarcocystis, Balantidium Coli, and Blastocystis* 2122  
*Rosemary Soave and Cynthia S. Weikel*
261. *Microsporidia* 2130  
*Ralph T. Bryan*

## SECTION H. DISEASES DUE TO HELMINTHS

262. *Introduction* 2134  
*Kenneth S. Warren*
263. *Intestinal Nematodes (Roundworms)* 2135  
*Adel A. F. Mahmoud*
264. *Tissue Nematodes (Trichinosis, Dracunculiasis, Filariasis)* 2140  
*David I. Grove*
265. *Trematodes (Schistosomiasis) and Other Flukes* 2145  
*Adel A. F. Mahmoud*
266. *Cestodes (Tapeworms)* 2151  
*Thomas C. Jones*
267. *Visceral Larva Migrants and Other Unusual Helminth Infections* 2157  
*Theodore E. Nash*

## SECTION I. ECTOPARASITES

268. *Introduction* 2162  
*Barbara Braunstein Wilson and Peyton E. Weary*
269. *Lice (Pediculosis)* 2163  
*Barbara Braunstein Wilson and Peyton E. Weary*
270. *Scabies* 2165  
*Barbara Braunstein Wilson and Peyton E. Weary*
271. *Maggots (Myiasis)* 2166  
*Barbara Braunstein Wilson and Peyton E. Weary*
272. *Mites (Including Chiggers)* 2167  
*Barbara Braunstein Wilson and Peyton E. Weary*
273. *Ticks (Including Tick Paralysis)* 2168  
*Barbara Braunstein Wilson and Peyton E. Weary*

## SECTION J. DISEASES OF UNKNOWN ETIOLOGY

274. *Roseola (Exanthem Subitum)* 2170  
*Anne A. Gershon*
275. *Kawasaki Syndrome (Mucocutaneous Lymph Node Syndrome)* 2171  
*Jacob A. Lohr*

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## PART IV. SPECIAL PROBLEMS

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### SECTION A. NOSOCOMIAL INFECTIONS

276. *Organization for Infection Control* 2176  
*Richard P. Wenzel*
277. *Isolation* 2180  
*Stephen A. Streed and Richard P. Wenzel*
278. *Sterilization, Disinfection, and Disposal of Infectious Waste* 2182  
*Michael A. Martin and Richard P. Wenzel*

103. Kean BH, Kimball AC. The complement-fixation test in the diagnosis of congenital toxoplasmosis. *Am J Dis Child*. 1977;131:21.
104. Naot Y, Barnett EV, Remington JS. Method for avoiding false positive results occurring in immunoglobulin M enzyme-linked immunosorbent assays due to presence of both rheumatoid factor and antinuclear antibodies. *J Clin Microbiol*. 1981;14:73.
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## 256. PNEUMOCYSTIS CARINII

PETER D. WALZER

*Pneumocystis carinii* was discovered in 1909 by Chagas who mistakenly interpreted the organism as a trypanosome. Several years later the Delanões identified *P. carinii* as a separate genus and species and named the organism in honor of Dr. Carini, another early worker. *Pneumocystis carinii* first came to medical attention when it was implicated as the cause of interstitial plasma cell pneumonia, a disorder of institutionalized debilitated infants of central and eastern Europe after World War II. In the 1960s *P. carinii* became widely appreciated as an important cause of pneumonia in immunocompromised hosts; however, with the development of safe and effective chemotherapy in chemoprophylaxis, interest in the organism waned. The 1980s witnessed a dramatic increase in the incidence of *P. carinii* pneumonia associated with the acquired immunodeficiency syndrome (AIDS). This has presented new clinical challenges and rekindled investigative interest in the organism.

### THE PATHOGEN

The taxonomy of *P. carinii* has long been a matter of controversy.<sup>1</sup> Most workers have classified the organism as a protozoan based on morphologic structural properties (e.g., ameboid appearance, presence of filopodia), lack of growth on fungal media, and sensitivity to antiprotozoal drugs. The words used to describe the life cycle stages of the organism have been based on terminology used for protozoa. Investigators favoring a fungal classification of *P. carinii* point to similarities to the ascospore formation in yeasts, the poorly developed organelle system, and the staining with methenamine silver and other reagents that stain fungi. Analysis of ribosomal RNA sequences of microorganisms has recently become an important tool for phylogenetic analysis; when applied to *P. carinii*, data suggest a closer relationship to fungi than to protozoa.<sup>2,3</sup> This has rekindled interest in the fungal characteristics of the organism.

*Pneumocystis carinii* exists as a saprophyte in the lungs of humans and a variety of animal species in nature. Organisms from these hosts have identical morphologic features, but antigenic as well as animal challenge studies suggest that species or strain differences exist.<sup>4,5</sup> Analysis of the life cycle of *P. carinii* has been based on morphologic studies of human or rat lung sections and, to a lesser extent, on organisms grown in tissue culture.<sup>6,7</sup> Three developmental stages of *P. carinii* have been identified. The trophozoite or trophic form, the most numerous stage, is small (1-4 µm), pleomorphic, and commonly exists in clusters. This form of the organism is identified on Giemsa stain by its reddish nucleus and blue cytoplasm (Fig. 1A). On electron micrographs there are a nucleus, mitochondria, a few other organelles, and tubular cytoplasmic extensions termed filopodia. The cyst is large (5-8 µm), has a thick wall, and contains up to eight daughter forms or intracystic bodies termed sporozoites. The cyst is easily recognizable by stains such as methenamine silver that stain its cell wall (Fig. 1B). The

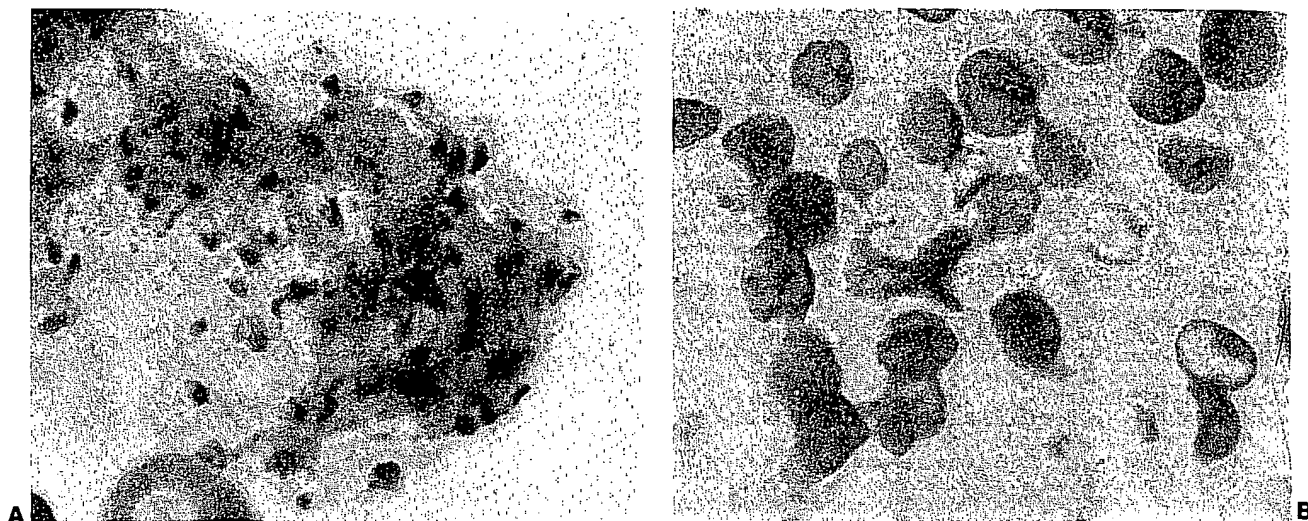


FIG. 1. (A) Cluster of *Pneumocystis carinii* trophozoites and cysts. (Diff-Quik,  $\times 2500$ ). (B) Cluster of *P. carinii* cysts. (Methenamine silver stain,  $\times 1250$ ).

precyst (4–6  $\mu\text{m}$ ) is an intermediate stage, but a definition of its morphologic features has varied among different investigators.

It is generally agreed that trophozoites multiply asexually, perhaps by binary fission. Trophozoites appear to develop into cysts by a sexual cycle, as illustrated by the presence of synaptonemal complexes in precysts. When the cyst reaches maturity, the sporozoites are liberated and then develop into trophozoites. Little is known about the specific factors or conditions that stimulate excystation or encystation of *P. carinii*.

Despite strenuous efforts by many investigators, only limited progress has been achieved with the *in vitro* cultivation of *P. carinii*.<sup>1</sup> Rat-derived organisms can be propagated on several different cell lines; under optimal conditions, a 10-fold increase in *P. carinii* can be obtained in primary culture and organisms can be serially passaged a few times to naive cultures. Little success has been achieved with human *P. carinii* or with any source of the organism using axenic media. A major impediment to *P. carinii* cultivation has been the lack of reproducibility and standardization among different laboratories. Nevertheless, the available systems have been helpful in studies of *P. carinii* life cycle, of susceptibility to antimicrobial agents, and as a purification step to obtain organisms free from host tissue contaminants.

Within the alveolus *P. carinii* adheres tightly to a specific lining cell, the type 1 pneumocyte,<sup>8</sup> but an intracellular stage in the life cycle has not been found. There is some evidence suggesting that *P. carinii* is covered by alveolar lining fluid and not necessarily in direct contact with inspired air. It seems likely that the organism obtains nutrients from the alveolar fluid constituents or lining cells. Little is known about *P. carinii*'s biochemical pathways; hypotheses have ranged from a metabolism of low-molecular-weight substances (based on the organism's primitive organelle system) to the occurrence of endocytosis. Experimental studies performed on nonreplicating organisms have suggested that *P. carinii* can utilize molecular oxygen and synthesize nucleic acids, proteins, carbohydrates, and phospholipids.<sup>9</sup> Histochemical staining has demonstrated the existence of several dehydrogenase enzymes.<sup>10</sup>

#### EPIDEMIOLOGY

Studies in immunosuppressed animals have shown that *P. carinii* is communicable and that the airborne route seems to be the major mode of transmission.<sup>11</sup> Questions about the infective

form or environmental sources of the organism, vectors, or definitive or intermediate hosts remain unanswered. Person-to-person transmission of *P. carinii* has been suggested by outbreaks and clusters of cases of pneumocystosis in orphanages and hospitals<sup>12</sup> and by the occurrence of the disease in immunosuppressed patients who have prolonged contact with each other. The incubation period is thought to be about 4–8 weeks. There is no evidence that *P. carinii* infection is a zoonosis.

*P. carinii* has a worldwide distribution. Seroepidemiologic surveys have demonstrated that most healthy children have been exposed to the organism by an early age.<sup>13</sup> Autopsy surveys have revealed subclinical *P. carinii* pulmonary infection in about 5 percent of patients with lymphoreticular neoplasms and rarely in healthy people.<sup>14</sup>

#### PATHOGENESIS AND PATHOLOGY

*Pneumocystis carinii* is of such low virulence that inoculation of organisms results in no observable damage to the host. However, such exposure does stimulate an immune response, and recent interest has focused on the use of the immunoblotting technique to delineate the specific antigens involved. A 116-kilodalton (kD) moiety has been found on the surface of *P. carinii* from rats, mice, humans, rabbits, and ferrets.<sup>15,16</sup> Other important rat *P. carinii* antigens are bands of about 45 and 50 kD, while by far the most prominent human *P. carinii* moiety is a broad-based band of about 40 kD.<sup>5</sup> Since these antigens are recognized by a variety of sources of antibody, they possess both shared as well as species-specific determinants. Biochemical data so far suggest that the antigens are composed of protein and carbohydrate constituents.<sup>17</sup>

The attachment of *P. carinii* to the type 1 pneumocyte plays a central role in the host-parasite relationship in this infection.<sup>8</sup> Ultrastructural studies have demonstrated that the surfaces of organism and host cells are closely apposed without fusion of cell membranes or changes in the intramembranous particles, but the specific factors involved in the mechanism of attachment (e.g., receptors, lectins) have not been defined. The surface of *P. carinii* and type 1 cells is rich in carbohydrates, and fluoresceinated lectin probes have revealed that glucose, mannose, and N-acetylglucosamine residues are prominent constituents.<sup>18</sup> Exposure to *P. carinii* does not result in protective immunity, suggesting that the organism possesses evasion mechanisms within the milieu of the alveolar micro-environment.

It is generally considered that impaired cellular immunity is more important than impaired humoral immunity in predisposing to *P. carinii* infection, although the specific host immune defects involved in the process are poorly understood. The patient populations at risk for pneumocystosis include premature, malnourished infants; children with primary immunodeficiency diseases (particularly severe combined immunodeficiency disease); and patients receiving immunosuppressive drugs for the treatment of cancers, organ transplantation, and other disorders.<sup>19</sup> Corticosteroids have been by far the most important form of immunosuppressive therapy; these agents not only lead to the development of pneumocystosis by themselves but also potentiate the effects of chemotherapy protocols involving other cytotoxic drugs. The relationship of corticosteroids to *P. carinii* has also been emphasized by reports of the occurrence of cases of pneumocystosis occurring in patients with Cushing syndrome.<sup>20</sup> The incidence of *P. carinii* pneumonia in different populations of compromised hosts can be directly related to the type and intensity of immunosuppression.<sup>21</sup> This has led to the hypothesis that development of overt disease in these patients represents reactivation of latent infection.

In the 1980s AIDS has become the most common underlying disease predisposing to the development of pneumocystosis.<sup>22</sup> *Pneumocystis carinii* pneumonia occurs in greater than 60 percent and perhaps up to 80–90 percent of AIDS patients in the United States during their lifetime and is the leading cause of mortality. The principal immunologic defect in AIDS is a reduction in number and function of CD4 T helper cells, although impaired function of other cell types also occurs. Blastogenic assays have demonstrated that most healthy adults have good proliferative responses to *P. carinii*, while patients infected with the human immunodeficiency virus (HIV) exhibit a progressive decline in response that parallels severity of this infection.<sup>23</sup> AIDS patients fail to exhibit any proliferative response to *P. carinii* even after recovering from pneumocystosis and receiving zidovudine (AZT) therapy. It is unclear whether the pathogenesis of pneumocystosis in AIDS and other immunodeficiency diseases represents simple reactivation of latent infection or perhaps involves additional exposure to exogenous sources of the organism.

Protein malnutrition is another important risk factor for *P. carinii* infection.<sup>24</sup> Protein malnutrition mainly inhibits cell-mediated immunity and in its most extreme form can induce the development of pneumocystosis under experimental conditions. A more subtle and yet clinically important role for malnutrition is as a complication of the patient's underlying disease or chemotherapy.

Systemic and local antibodies develop in response to *P. carinii* infection and appear to be mainly of the IgG class.<sup>1</sup> Although pneumocystosis has occurred in children whose primary immunodeficiency disease has been characterized mainly by impaired B-cell function, the presence of antibodies has not prevented the development of *P. carinii* pneumonia induced by immunosuppression. Antibodies enhance phagocytosis of *P. carinii* by alveolar macrophages and thereby may function as opsonins.<sup>25</sup> Once engulfed by the macrophage, the organism is immediately digested.

Animal models have been very helpful in studying the pathogenesis, diagnosis, and treatment of pneumocystosis.<sup>26</sup> Rats, mice, rabbits, guinea pigs, and ferrets administered corticosteroids for about 8 weeks spontaneously develop *P. carinii* pneumonia with histologic features identical to those in the human form of the disease. The mechanism here appears to be reactivation of latent infection, since immunosuppressed animals without environmental exposure to *P. carinii* fail to develop the disease.

Sequential studies in the rat model have revealed that *P. carinii* organisms propagate slowly and gradually fill alveolar lumens; at the peak intensity of infection, each lung may contain  $10^9$ – $10^{10}$  organisms. This process is accompanied by the de-

velopment of the typical foamy alveolar exudate and a series of changes on electron microscopy that culminate in damage to the type 1 cell.<sup>8</sup> There are also alterations in respiratory mechanics and surfactant phospholipids that contribute to this overall picture of diffuse alveolar injury.<sup>27</sup> Host inflammatory changes are inconspicuous and are characterized mainly by hypertrophy and hyperplasia of type 2 pneumocytes (a typical reparative response). Studies of lymphocyte surface markers have revealed a decline in CD4 helper cells in peripheral blood in the lungs but not at other body sites during the development of pneumocystosis in this animal model.<sup>28</sup>

When corticosteroids are withdrawn, the rat regains its weight and mounts a vigorous inflammatory and immune response to clear *P. carinii* from the lung. Alveolar macrophages become very prominent in the phagocytosis of the organism. There also occur a heavy mononuclear cell infiltrate in the lung, the return of T-cell subsets to normal levels, the formation of serum antibodies to *P. carinii*, and the development of pulmonary interstitial fibrosis. Yet, even with the restoration of normal immune function, a few *P. carinii* organisms can be found attached to type 1 cells.

Cases of *P. carinii* pneumonia have occurred spontaneously in a variety of animals with suspected or proved immunodeficiency diseases.<sup>26</sup> Outbreaks of pneumocystosis have been noted in colonies of athymic (nude) and scid mice, providing opportunities to study the pathogenesis of the disease in an immunodeficient animal population under natural conditions.<sup>29</sup> The clinical manifestations of *P. carinii* pneumonia are more severe in older than in younger mice. Once established within an animal colony, the organism may persist for many years. It might seem that these immunodeficient mice would be a good experimental model system, yet attempts to produce pneumonia with exogenous organisms have had conflicting results.

The pathologic features of pneumocystosis in humans reveal densely consolidated lungs with reddish grey cut surfaces. On histologic sections stained with hematoxylin and eosin, the alveoli are filled with pink frothy honeycombed material (Fig. 2); staining with methenamine silver demonstrates masses of organisms. Infants with interstitial plasma cell pneumonia display a prominent plasma cell infiltrate. By contrast, immunosup-

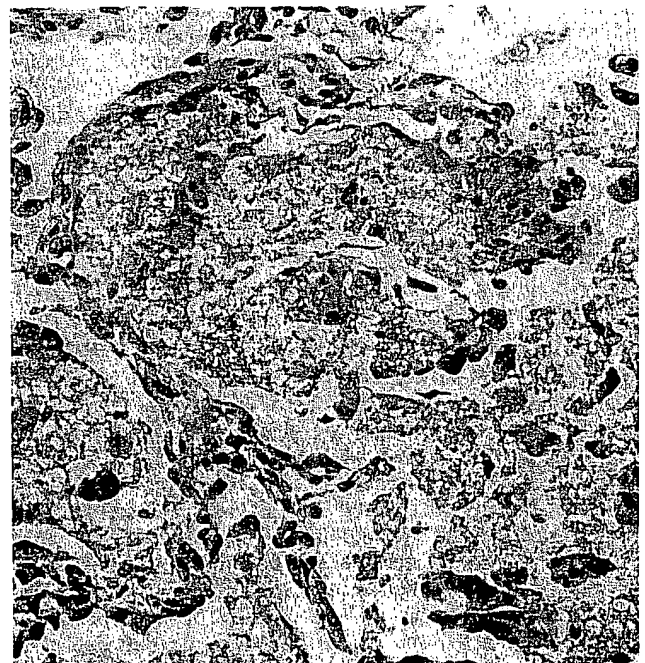


FIG. 2. *Pneumocystis carinii* pneumonia illustrating frothy honeycombed material filling alveolar space. (H&E,  $\times 165$ ).



pressed patients usually only demonstrate interstitial thickening resulting from hyperplasia and hypertrophy of type 2 cells, edema, and a scanty mononuclear cell infiltrate. A variety of atypical histologic features may also be present,<sup>30</sup> but it is not usually possible to determine whether they are due to *P. carinii* or to other conditions that damage the lung.

## CLINICAL MANIFESTATIONS

Interstitial plasma cell pneumonia has occurred classically in debilitated infants age 6 weeks to 4 months housed in orphanages or foundling homes under crowded conditions.<sup>31</sup> The disease begins insidiously with symptoms such as poor feeding and progresses gradually to overt respiratory distress and cyanosis. Cases sometimes occurred in explosive outbreaks, giving rise to the term "epidemic" form of *P. carinii* pneumonia. Interstitial plasma cell pneumonia has largely disappeared from industrialized countries but still exists in parts of the world (and in their refugees) where poor socioeconomic conditions abound.<sup>32</sup>

The presenting symptoms of *P. carinii* pneumonia in the compromised host include shortness of breath, fever, and a non-productive cough.<sup>19</sup> Patients receiving immunosuppressive drugs frequently develop these clinical manifestations after the corticosteroid dose has been tapered and are typically sick for about 1–2 weeks before seeking medical attention. Pneumocystosis in AIDS patients may be a more subtle disease with symptoms lasting from weeks to months.<sup>22,33</sup> On physical examination, tachypnea and tachycardia are frequently present in acutely ill patients. Children may demonstrate cyanosis, flaring of the nasal alae, and intercostal retractions in severe disease. Lung auscultation is usually not helpful, although rales can be heard in about one-third of adults with the disease.

The peripheral blood leukocyte count more likely reflects the patient's underlying disease or immunosuppressive therapy rather than the activity of *P. carinii*. Serum albumin levels may be low if malnutrition is present. The chest roentgenogram classically exhibits bilateral diffuse infiltrates extending from the perihilar region (Fig. 3). In some cases the chest roentgenogram may be completely normal or show such atypical findings as nodules, cavitation, or pneumatocele.<sup>1</sup> There may also be increased lung uptake on gallium scan and enhanced clearance of inhaled technetium 99m diethylenetriamine pentaacetate (tcDPA), a marker for alveolar–capillary membrane permeability.<sup>34,35</sup> Blood gases reveal hypoxemia, increased alveolar–arterial oxygen and gradient, and respiratory alkalosis; in the later stages of *P. carinii* pneumonia, a respiratory acidosis may develop. Pulmonary function abnormalities include impaired vital capacity, total lung capacity, and diffusing incapacity.<sup>36</sup> In general, the changes in blood gases in pulmonary function tests are less severe in AIDS patients than in other immunosuppressed patients.

## DIAGNOSIS

Pneumocystosis should be considered in any immunocompromised patient who develops respiratory symptomatology, fever, and an abnormal chest roentgenogram. Since these clinical manifestations may be produced by a long list of infectious and noninfectious agents, diagnosis of *P. carinii* must be made by histopathologic demonstration of the organism.<sup>37</sup> Two basic types of stains have been used. Reagents such as methenamine silver or one of its simpler variants (e.g., toluidine blue O, cresyl echt violet, Gram–Weigert), which selectively stain the wall of *P. carinii* cysts, have been popular among pathologists because they can be used on imprint smears or tissue sections and are easy to interpret. These reagents provide no data about the status of the internal cyst contents; since fungi are also stained, it is possible that these organisms could be confused with *P. carinii* in cases of light infection. The other group of stains,

typified by Giemsa or one of its variants (e.g., Diff-Quik, polychrome methylene blue), stain *P. carinii* trophozoites, intracystic bodies, and intermediate forms in imprint smears but cannot be reliably applied to tissue sections. These reagents are rapid and easy to perform, but since they also stain host cells, they require more experience for proper interpretation.

The impact of AIDS has not only increased the proficiency of clinical laboratories in diagnosing *P. carinii* by standard techniques but has also stimulated the development of alternative approaches. Examples include the use of the Gram stain, Wright stain, Papanicolaou smears, and stains such as acridine orange or propidium iodide which are used with fluorescence microscopy. There is increasing attention being devoted to the examination of *P. carinii* in fresh specimens by using phase contrast or Normarski interference contrast microscopy.<sup>38</sup> These techniques provide excellent views of the developmental stages of the organism, and when combined with the use of a vital dye such as erythrosin B, might be very helpful in evaluating organism viability and the effects of chemotherapy. *P. carinii* can be readily detected by immunofluorescent or immunoperoxidase staining (Fig. 4); with the development and commercial availability of monoclonal antibodies, these techniques might gain more widespread clinical application.<sup>39</sup> Now that cloned DNA sequences from the organism are available,<sup>40,41</sup> filter hybridization of clinical specimens can be evaluated as a diagnostic tool.

The collection of specimens that accurately reflect the disease process in the lungs is an essential component of the diagnostic evaluation of patients with suspected pneumocystosis. The infrequent presence of *P. carinii* in sputum or tracheal secretions has severely limited the use of these specimens in non-AIDS patients.<sup>19</sup> However, recent studies have shown that the diagnosis of *P. carinii* can be made in a high proportion of AIDS patients by examination of sputum that has been induced by inhalation of a saline mist.<sup>39</sup> This probably reflects the higher organism burden in patients with AIDS, but quantitative *P. carinii* counts in different patient groups are lacking. It remains to be determined whether reduced sputum will retain its high diagnostic value in routine clinical practice; nevertheless, it represents a simple, noninvasive, and inexpensive screening procedure.

Fiberoptic bronchoscopy is the most commonly used diagnostic procedure in use in adults today.<sup>42</sup> Bronchoalveolar lavage has generally replaced washings and brushings and causes few serious complications. Transbronchial biopsy may be helpful in some patients but is a more invasive procedure with higher morbidity. The diagnosis of pneumocystosis can usually be established by fiberoptic bronchoscopy in over 90 percent of AIDS patients, although the yield from this procedure in non-AIDS patients is probably not quite as high.

Open lung biopsy, which requires the use of operating room facilities and general anesthesia, has long served as the standard reference procedure for the diagnosis of *P. carinii* because it provides the greatest amount of tissue that can be obtained under direct visualization. Open lung biopsy is performed less frequently than in the past, and there is some controversy over its role in the diagnostic evaluation of lung infiltrates in immunosuppressed patients.<sup>43</sup> I believe that open lung biopsy should be used when bronchoscopy is nondiagnostic or when a patient being treated for *P. carinii* is suspected of having another infection or condition contributing to pulmonary problems. Open lung biopsy has been shown to be superior to transbronchial biopsy when both procedures are performed simultaneously in the same patients<sup>44</sup> and has also been helpful in detecting conditions such as Kaposi's sarcoma of the lungs that have been difficult to diagnose by other techniques.<sup>45</sup>

Needle aspiration or biopsy of the lung was once quite popular but is now usually performed only in children. Enthusiasm for the procedure in adults has waned because of low diagnostic yield and high rate of complications.

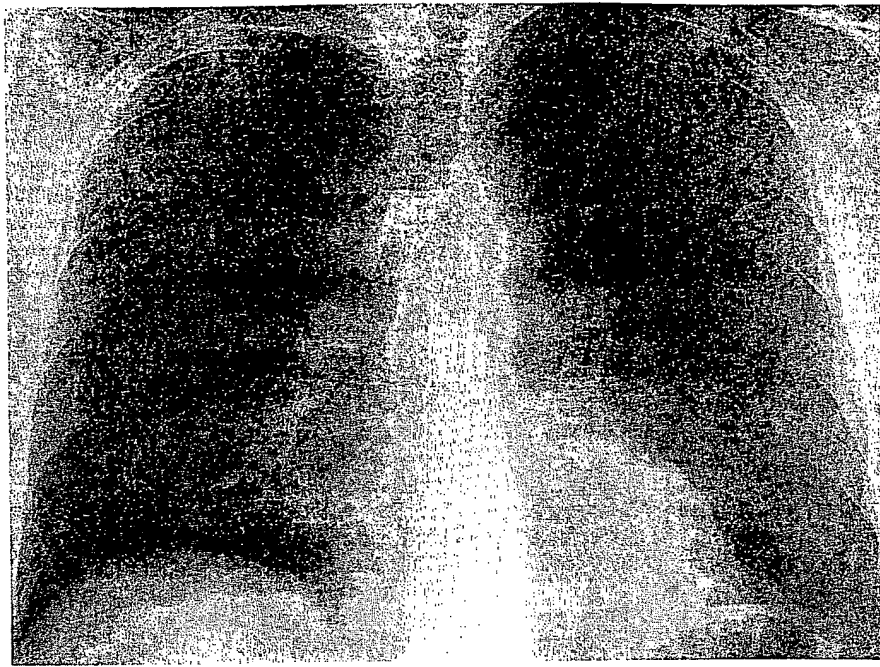


FIG. 3. Chest roentgenogram showing bilateral infiltrates of *P. carinii* pneumonia.

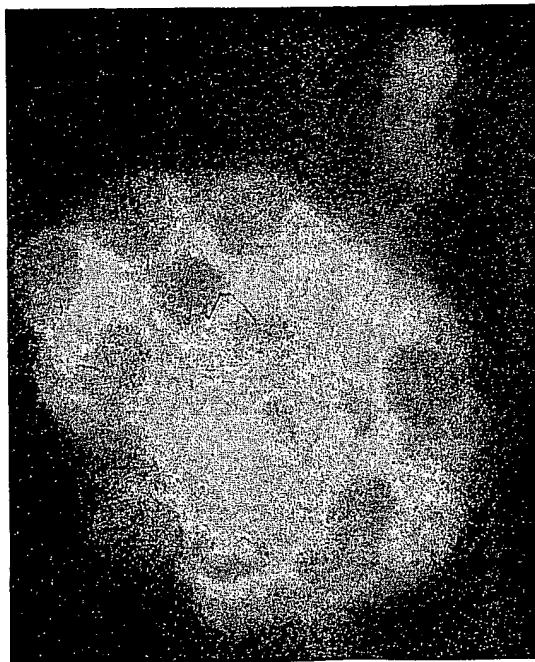


FIG. 4. Clusters of *P. carinii* cysts stained by immunofluorescence. Note peripheral rim pattern of staining. ( $\times 1250$ )

The diagnosis of pneumocystosis should be pursued in an aggressive and systematic manner. Close cooperation is needed among the patient's primary physician, consultants, and clinical laboratories to ensure proper collection and analysis of specimens. Invasive procedures should be performed early in the patient's course to lessen the risk of complications.

Attempts have been made to detect circulating *P. carinii* antigens in serum by counterimmunoelectrophoresis or latex agglutination techniques.<sup>46</sup> Unfortunately, these systems have lacked sufficient sensitivity, specificity, and reproducibility to

be of clinical diagnostic value. Serum antibodies to *P. carinii* have been measured by complement fixation, the indirect fluorescent antibody (IFA) technique, and enzyme-linked immunosorbent assay (ELISA) with whole organisms or soluble extracts as the antigen; the high prevalence of serum antibodies to *P. carinii* in the general population has limited the value of these serologic techniques in the diagnosis of pneumocystosis.<sup>13,47</sup> Perhaps measurement of serum antibodies to specific *P. carinii* antigens will be a more fruitful technique.<sup>48</sup>

#### TREATMENT

*Pneumocystis carinii* infection in normal hosts is not known to cause symptoms, and thus no treatment is necessary. Untreated pneumocystosis in the form of interstitial plasma cell pneumonia has a mortality rate of about 50 percent, while the disease in the immunocompromised host is almost always fatal. The hospital course is one of progressive hypoxemia and respiratory insufficiency. A variety of factors affect the success of the therapy of *P. carinii* pneumonia including the severity of the disease, prior lung damage, leukocyte or lymphocyte count, the presence of other opportunistic infections, and the status of the patient's underlying medical condition and nutrition.<sup>19,33,49</sup> The need for ventilator support, which is associated with an ominous prognosis, has raised difficult medical and ethical questions for AIDS patients and their physicians about whether to institute such measures.<sup>50</sup>

Dissemination of *P. carinii* beyond the lungs is uncommon but has been well documented (at least 20 cases have been reported in the literature).<sup>51</sup> Recent reports have focused on AIDS patients, although it is unknown whether the extrapulmonary spread of *P. carinii* in this patient population is more frequent than in other immunocompromised hosts. The mechanism of spread of the organism appears to be by hematogenous or lymphatic routes or both. Major sites of extrapulmonary involvement have included lymph nodes, bone marrow, spleen, and liver, but a variety of other locations (e.g., ear, eye, gastrointestinal tract) have also been reported. The presence of *P. carinii* in these locations has usually been suspected by the dem-



onstration of the typical foamy honeycombed material by hematoxylin and eosin stain.

Since the mid-1970s, the major drugs used in the therapy of pneumocystosis have been trimethoprim-sulfamethoxazole (TMP-SMX) and pentamidine isethionate. These drugs are equally effective in patients with AIDS and in other populations of immunocompromised hosts; they have an overall success rate of about 70–80 percent, but even higher rates can be achieved if *P. carinii* pneumonia is mild and therapy is begun promptly.<sup>22,33,52–54</sup>

TMP-SMX exerts its antimicrobial effect on other organisms by inhibiting folic acid synthesis; data obtained so far suggest a similar mechanism of action of *P. carinii*.<sup>55</sup> TMP-SMX is administered orally or intravenously in a dose of 20 mg/kg per day TMP and 100 mg/kg per day SMX in four divided doses. The parenteral route should be used in patients who are very ill or who have gastrointestinal disturbances. The dose of TMP-SMX should be adjusted to achieve optimal serum levels of TMP of 5–8 µg/ml in adults and 3–5 µg/ml in children and levels of SMX of 100–150 µg/ml. The drug is administered for 14 days to non-AIDS patients and is usually well tolerated. Side effects are characterized mainly by gastrointestinal complaints and skin rashes.

Pentamidine isethionate, a diamidine, is an old drug that was first used in the treatment of African trypanosomiasis. Its mechanism of action against *P. carinii* is unknown. Pentamidine isethionate is administered parenterally in a single dose of 4 mg/kg per day for 14 days in non-AIDS patients. The intravenous route has proven to be no more toxic than the intramuscular route<sup>56</sup> and seems to be the preferred method of administration by most clinicians. Pentamidine isethionate is diluted in 50–250 ml of a 5% dextrose solution and infused over at least a period of 1 hour. Pharmacokinetic studies have indicated that serum levels of pentamidine isethionate are quite low even in the presence of moderate renal impairment but may accumulate with repeated dosing; the drug can be found bound to tissues even many months after administration has been stopped.<sup>57,58</sup> Pentamidine isethionate is a toxic drug as evidenced by the fact that side effects occur in about half of non-AIDS patients.<sup>19</sup> These include hypotension, dizziness, cardiac arrhythmias, azotemia, hypocalcemia, hepatic disturbances, and problems at the sites of intramuscular injection. Hypoglycemia may occur and can be followed at a later date by the development of hyperglycemia or frank diabetes mellitus.

Non-AIDS patients respond to the therapeutic effects of TMP-SMX and pentamidine isethionate in a similar manner. Clinical improvement is usually noted after about 4 days of treatment, although there is some variation among individual patients; if there is no response after 5–6 days, it is wise to consider switching to another drug.

The treatment of *P. carinii* pneumonia in patients with AIDS is more complex. These individuals tend to take a longer time before showing a clinical response, and thus it has become customary to administer drugs for 21 days and wait at least 7 days before concluding there is a treatment failure. Even when there has been a clear-cut clinical response, at least half of the AIDS patients will have *P. carinii* present in bronchoalveolar lavage fluid after a course of therapy.<sup>53,59</sup> The specific life cycle stages, viability, and clinical significance of these organisms have not been studied in detail. In contrast to other immunocompromised hosts, patients with AIDS have a high rate of recurrence (about 50 percent) of pneumocystosis that has not been materially altered by drugs (e.g., AZT) that have activity against HIV; it is unclear whether these recurrences represent relapse or true reinfection. Some patients may experience multiple episodes of *P. carinii* pneumonia. It is generally thought that these repeat bouts of the disease are more difficult to treat than the initial episode, but controlled studies are lacking.

A major impediment to *P. carinii* therapy in AIDS is the high frequency of intolerance to antimicrobial drugs.<sup>22,33,53,54</sup> Most

patients experience adverse reactions to TMP-SMX that include skin rash, fever, leukopenia, thrombocytopenia, and hepatic dysfunction; these problems usually begin during the second week of therapy and are often of sufficient severity to require discontinuation of the drug. The side effects are generally considered to represent a form of hypersensitivity reaction directed mainly toward the sulfonamide component, but the mechanisms involved are poorly understood. Since substitution of another sulfonamide or sulfone or rechallenge with TMP-SMX has led to widely disparate results in these patients, such actions should only be undertaken with great caution. Adverse reactions to pentamidine isethionate among AIDS patients are generally similar to those among other compromised hosts except that certain side effects are more common (neutropenia) or are particularly troublesome (hypotension, hypoglycemia). Low blood glucose may occur during or after completion of pentamidine isethionate therapy, and clinical manifestations range from an abnormal laboratory finding to life-threatening coma.<sup>60</sup>

The wide experience with TMP-SMX and pentamidine isethionate over the past several years has allowed the formulation of general guidelines for their use. TMP-SMX is the preferred therapy for *P. carinii* pneumonia in non-AIDS patients because of its better tolerance. There is no clear-cut drug of choice in patients with AIDS, but TMP-SMX is probably preferred by most physicians because of its availability in oral and parenteral forms, well-known pharmacokinetics, and broad antibacterial spectrum. Combination therapy with TMP-SMX and pentamidine isethionate is no more effective than either agent used alone and may increase the risk of adverse effects. If one of these drugs has achieved a good clinical anti-*P. carinii* response but has to be discontinued because of toxicity, the other drug is also likely to be effective; however, if one of these drugs has to be withdrawn because of a poor therapeutic response, the second drug is also likely to be ineffective.

A variety of other therapeutic regimens are currently being explored. Rationale for these approaches has come from data obtained in the rat model of pneumocystosis, which has been a reliable predictor of drug activity in humans.<sup>4,61–63</sup> Unfortunately, none of these treatment protocols have been subjected to rigorous controlled clinical trials, and thus conclusions about their value must remain tentative. Most of the attention has focused on inhibitors of folic acid synthesis. Trimetrexate, a lipid-soluble derivative of methotrexate and a potent dihydrofolate reductase (DHFR) inhibitor, has shown promising results in the treatment of pneumocystosis when used alone or in combination with a sulfonamide; bone marrow toxicity can be ameliorated by the administration of high doses of folinic acid.<sup>55,64</sup> Combinations of pyrimethamine and sulfadiazine and trimethoprim and dapsone have been successful in treating small numbers of patients.<sup>65,66</sup> Dapsone has anti-*P. carinii* activity when used alone and may be better tolerated by AIDS patients than are sulfonamides. Since a variety of DHFR inhibitors, sulfonamides, and sulfones are undergoing evaluation, it will be important to determine which compounds offer the greatest value in terms of efficacy and toxicity.

Another interesting therapeutic approach involves the administration of pentamidine isethionate by aerosol, which results in selectively high concentrations of the drug in the lungs.<sup>67</sup> Aerosol pentamidine has mainly been used in patients with mild forms of pneumocystosis and appears to be well tolerated. This form of administration has stimulated interest in determining whether lower parenteral doses of pentamidine isethionate might be used and still be effective.<sup>68</sup>  $\alpha$ -Disfluoromethylornithine (DFMO), an inhibitor of polyamine biosynthesis with antitrypanosomal properties, has shown promising results in the treatment of *P. carinii* pneumonia in patients who have failed or could not tolerate standard forms of therapy.<sup>69</sup> Other agents that have shown anti-*P. carinii* activity in animal model or tissue culture systems include diamidines and related compounds

(e.g., diminazine, amidocarb, quinapyramine), purine nucleosides (9-deazainosine), and a combination of clindamycin and primaquine.<sup>70-72</sup> Therapy is also discussed in Chapter 110.

General supportive measures such as maintaining adequate oxygen, careful fluid balance, and nutrition are an important part of the management of patients with pneumocystosis. There is controversy over the use of corticosteroids as adjunctive treatment because of the belief that host inflammatory response may be playing a role in the pathogenesis of the pneumonia.<sup>1</sup> In patients who are receiving immunosuppressive drugs for the treatment of cancer or other disorders, it seems prudent to taper steroids and related drugs to the lowest level permitted by the underlying disease. Although some studies have suggested that the administration of corticosteroids is helpful in selected AIDS patients,<sup>73</sup> I believe that the serious side effects of these agents outweigh their empiric use until benefits can be clearly demonstrated from controlled clinical trials.

The long-term follow-up of patients who survive one or more episodes of *P. carinii* pneumonia is beginning to receive attention. Residual pulmonary function abnormalities have been demonstrated in adults but not in children.<sup>74,75</sup> Pulmonary fibrosis can also occur,<sup>76</sup> but since the lung may be subjected to a variety of insults during intensive therapy of pneumocystosis, the precise role of *P. carinii* needs further clarification.

## PREVENTION

Recovery from *P. carinii* pneumonia is not accompanied by the development of acquired immunity, and thus the patient is at risk of developing recurrences of the disease as long as the predisposing or immunosuppressive conditions exist. Prospective studies have shown that the administration of TMP-SMX in a dose of 5 mg/kg per day TMP and 25 mg/kg per day SMX administered daily or three times a week can prevent the development of pneumocystosis in immunosuppressed patients.<sup>77</sup> Since the drug does not kill *P. carinii*, it is only effective as a prophylactic agent as long as it is being given.<sup>78,79</sup> Patients usually tolerate the long-term administration of TMP-SMX quite well, but it is still prudent to carefully consider the risks and benefits before starting on such an endeavor. Serious adverse reactions have occurred in renal transplant recipients who were taking other immunosuppressive drugs.<sup>80</sup> Prophylactic TMP-SMX has been shown to be effective in AIDS patients in one prospective but uncontrolled study.<sup>81</sup> However, the toxicity of this and other sulfonamide regimens appears to be quite high.<sup>82</sup> Aerosol pentamidine is a more promising approach,<sup>83</sup> but controlled trials are needed.

Since *P. carinii* may be communicable from person to person, it is prudent in the hospital setting to isolate patients with active disease from direct contact with other susceptible hosts. No official guidelines have been developed, but the most common measures have included use of a private room or respiratory isolation.

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## 257. GIARDIA LAMBLIA

DAVID R. HILL

*Giardia lamblia*, a flagellated enteric protozoan, has emerged in recent years as an important cause of endemic and epidemic diarrhea. Its wide distribution throughout the world makes it an important contributor to chronic debilitating diarrheal illnesses and to diarrhea in travelers. In the United States it is the most prevalent enteric parasite and is the leading infectious agent identified in waterborne outbreaks of diarrhea.

### DESCRIPTION OF THE PATHOGEN

The genus *Giardia* belongs to the order Diplomonadida and the family Hexamitidae. Separate mammalian hosts were once considered to harbor different *Giardia* species; however, to date only three species have been identified and these primarily by morphologic criteria. They are designated *G. lamblia* (also called *intestinalis* or *duodenalis*), infecting humans and other large mammals, *G. muris*, found in rodents and *G. agilis*, found in frogs.<sup>1</sup> Analysis of *G. lamblia* antigens, isoenzyme patterns, and DNA has allowed a more sophisticated grouping of *Giardia*.<sup>2</sup> These studies, as well as the clinical differences between isolates in experimental human infection, make it clear that both strain and antigenic variation occurs.<sup>3a,3b</sup>

The life cycle of *G. lamblia* comprises two stages: the trophozoite, or freely living stage, and the cyst. The trophozoite

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